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Solubility Enhancement of Poorly Water Soluble Drug Using Mesoporous Silica as Carrier

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ABSTRACT
Oral drug delivery (ODD) is the most preferred and convenient route of drug administration due to high patient compliance, cost-effectiveness, least sterility. All orally administered drugs must dissolve in the aqueous medium of the gastrointestinal tract before being absorbed.According to the Biopharmaceutical Classification System (BCS), low solubility and low bioavailability are problems for Class II drugs. Low solubility, rather than osmosis, is the rate-limiting step of absorption. The solubility and bioavailability of BCS class II drugs have been improved through various drug formulation development strategiesAdsorption on mesoporous silica has been shown to have significant potential to improve the solubility of low solubility drugs. Mesoporous materials have been widely used as carriers for controllable drug delivery due to their unique pore size, large surface area, and pore volume. Various mesoporous materials have been used in drug loading and release profiles, including M41S, SBA, MSU, and HMS. The large surface area and good material compatibility lead to the widespread use of porous silica in adsorption, enzyme immobilization and drug delivery. Bioactive substances can be incorporated into silica gel using the recently discovered sol-gel technique.
Keywords: -Adsorption, Cyclodextrins, Enzyme immobilisation, Mesoporous Silica.

I. INTRODUCTION: -

Oral solid dosage forms are the simplest, very popular as well as easy route for administration. Recently greater than forty percent of new drug molecules are identified as scantily water- soluble drugs. Among the various drug delivery routes, the oral pathway has attracted the most attention due to its unique advantages, including sustained & controlled delivery, ease of administration, feasibility for solid formulations, patient compliance & intensified immune response in case of vaccines.When an active substance is administered orally, it must first dissolve in the stomach and/or intestines before it can pass through the GI tract's membranes and enter the bloodstream. As a result, a medicine with low water solubility would usually display restricted absorption due to dissolving rate, and a drug with poor membrane permeability will usually exhibit limited absorption due to penetration rate. Poorly water-soluble compounds continue to be difficult to transform into useful pharmaceuticals. A complex network of physical-chemical, biological, physiological, and anatomical variables that operate alone and in concert to restrict medication bioavailability is what stands in the way of their effective oral administration. [(1)]

The Biopharmaceutics Classification System (BCS) divides drugs into four groups as follows: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability). A drug substance is considered highly soluble when the highest single therapeutic dose is soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8 at 371 °C.Permeability is evaluated on the basis of the extent of absorption of a drug from human pharmacokinetic studies. Alternatively, in vitro culture methods can also be used to predict drug absorption in humans. A drug is considered highly permeable when the absolute BA is 85%. High permeability can also be concluded if≥ 85% of the administered dose is recovered in urine as unchanged (parent drug) , or as the sum of parent drug, . Phase 1 oxidative, and Phase 2.[(2)]

Among four groups, drugs belonging to Class II and IV exhibit poor aqueous solubility, resulting in poor BA. Therefore, enhancing solubility. resulting in poor Bioavailability. Therefore, enhancing solubility and bioavailability of poorly water-soluble drugs in BCS Class II and IV is a significant challenge in the pharmaceutical industry. Drugs that have low solubility are Biopharmaceutics classification system (BCS) class II drugs, eg, phenytoin, danazol, nifedipine. In

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order to find the best solutions for the oral bioavailability concerns, the BCS classifies drugs intended for oral administration into 4 different groups based on the aqueous solubility/dissolution as well as the intestinal epithelium permeability. In class 1, drugs with both, high permeability and high solubility are found; those with high permeability but low solubility are assigned to class2 drugs with low permeability, but high solubility are classified as class 3, and finally, class 4 houses the drugs with both low solubility and low permeability. Based on the Noyes-Whitney equation, the dissolution rate is directly proportional to solubility, it is not considered as an independent determinant in BCS.[3]

According to the IUPAC definition, solubility is determined as "the analytical composition of a mixture or solution which is saturated with one of the components of the mixture or solution, expressed in terms of the proportion of the designated component in the designated mixture or solution. The solubility of a chemical substance depends on various parameters, mainly including the chemical nature of the solute, solvent, and co-existing agents within the dissolution medium, temperature and pressure. Commonly, solubility is expressed as mass per unit volume. The United States Pharmacopeia (USP) uses descriptive terms like freely soluble or practically insoluble to express the extent a drug can be dissolved in a solvent. These terms describe how many parts of solvent are required to solubilize one part of solute. [3]

Poor water solubility influences significantly a number of stages during the drug development and pre-clinical studies. A compound with aqueous solubility< 100 µg/mL is usually considered to have a dissolution- limited resorption. Simply increasing the drug amount in the oral dosage form however may lead to several problems. First, formulating a tablet with a high amount of drug may lead to poor powder properties. The powder might become sticky, have poor flowing properties, and higher costs in the development stage due to increased consumption of the drug. In in vitro screening, poor water solubility might result in precipitation and false outcomes can have consequences like underestimated activity and toxicity. In vivo, the high drug load could cause local irritations in the GI-tract and lead to lesser compliance, and ultimately, still not high enough plasma concentrations would result in.With these significant hurdles hampering the efficient development of the majority of new drug candidates, new and more efficient approaches for overcoming the poor aqueous solubility and low dissolution rates are of critical importance. For class 2 drugs, a variety of techniques exist to enhance their water solubility.[3]

Methods for solubility and dissolution enhancement: -[4]

Solubility and/or dissolution rate can be improved by physical, chemical, or other modifications on the drug molecules. A large variety of techniques exist to overcome poor water solubility of the drugs. Physical modification includes manipulation of the particle size, using different polymorphs of a drug, or solid solutions. Chemical modifications include variation of the pH, derivatization, or salt formations, among others. These approaches can be grouped into solubility improvement on the molecular level, solubility improvement on the colloidal level, and solubility improvement on the particle size level.On the molecular level, solubility can be improved by using co-solvents, using salt-forms of the drug, creating prodrugs, or using Cyclodextrins. On the colloidal level the solubility is increased by emulsions, microemulsions, or lipid based water-free formulations. The solubility enhancement on the particulate level includes nanosizing, or by the creation of metastable polymorphs.

I) Cyclodextrins: -

On the molecular level, solubility can be improved by using co-solvents, using salt-forms of the drug, creating prodrugs, or using cyclodextrins. On the colloidal level the solubility is increased by emulsions, microemulsions, or lipid based water-free formulations. The solubility enhancement on the particulate level includes nanosizing, or by the creation of metastable polymorphs. Cyclodextrins are molecular donut-shaped structures consisting of several glucose molecules. Cyclodextrins are mainly used to enhance the solubility of BCS class II drugs, but they also add stability to the drug via preventing chemical degradation. Furthermore, bioavailability is enhanced and adverse drug reactions are reduced (reduces irritations, like local drug delivery to the eye) However, solubility enhancement with cyclodextrins is restricted by their cavity size: the alpha form does not provide sufficient space for many drug molecules, and the larger gamma form is comparably expensive.

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II) Emulsions: -

Emulsions have been widely used to deliver drugs topically or systemically. An emulsion contains a hydrophilic and a hydrophobic phase. Depending on the formulation, the oil-in-water emulsion contains oil droplets that are stabilized in the water phase with surfactants, whereas a water-in-oil emulsion consists of water droplets in the (continuous) oil phase. The oil phase in emulsions facilitates the solubility of lipophilic drugs. Emulsions are meta-stable formulations, which is one of their main drawbacks. They are thermodynamically non-stable, thus needing mixing or shaking before administration. The relatively high surface energy of (small) droplets in the continuous phase can be stabilized to a certain extent with surfactants, but they can still coalesce over time. One possibility to overcome this problem is spray drying, where an emulsion is transformed into a dry powder emulsion. Apart from "classical" emulsions, so-called self-emulsifying systems can also help to improve the solubility dramatically, when no physical energy input is needed to create an emulsion (i.e. a spontaneous process when mixing all the components), the term selfemulsifying drug delivery system (SEDDS) is used. Depending on the droplet size, SEDDS can be further classified into self-microemulsifying drug delivery systems (SMEDDS) with the typical droplet size of 100 nm to 250 nm and self-nanoemulsifying drug delivery systems (SNEDDS) with an even smaller droplet size below 100 nm. SMEDDS and SNEDDS can be further differentiated by the stability mechanism. SMEDDS are formulated with a surfactant (normally water-soluble) and a co-surfactant (normally lipophilic), which both reduce the interfacial tension to form an isotropic, thermodynamically stable system.

III) Nanosizing: -

A nanosuspension is defined as a colloidal dispersion. The dispersant, i.e. the solid dispersed in a liquid, consists of small drug particles with a size below 1 μm. The size reduction of the crystals leads to an increase in the specific surface area. In consequence, the dissolution is enhanced, as compared to bulk (larger) crystals. To obtain these tiny drug particles, physical downsizing like milling or high-pressure homogenization as well as physicochemical methods such as precipitation, i.e., controlled recrystallization have been attempted with more or less success. Mostly, nanosuspensions are used for bioavailability enhancement of water-insoluble compounds. Other approaches like the use of lipidic systems can also enhance the water solubility of such compounds, however, nanosuspensions additionally improve the water solubility of so-called "brickdust" candidates, which are neither soluble in water. Nanosizing has the additional advantage that the drug crystals are dense and hence, high dosing can be achieved as compared to Cyclodextrins. The challenges of the nanosizing process consist of the high energy needed for down-sizing and obtaining polydispersed particles rather a monodisperse sample, thereby issues with heterogenicity in solubility and dissolution rate within the same batch. When decreasing the size, particle aggregation is another problem that decreases the drug solubility, because the surface area might be reduced dramatically in aggregates as compared to the primary drug particles. The latter can be partly avoided by lowering the surface energy via adding surfactants to the milling process. Especially charged polymers can enhance the colloidal stability of the drug particles due to the electrostatic repulsions. Instead, polymeric stabilizers can be used and mitigate steric stabilization of the drug particles as charged polymers can cause toxicity. Milling furthermore can affect the drug's crystalline status. During the milling process, the drug can be transformed into an amorphous state, which results in enhanced solubility and dissolution rate. The amorphous state is not a stable state, therefore, the drug can transform back into its crystalline state after milling.

Mesoporous Silica [5,6]

Utilization of inorganic mesoporous materials in formulations of poorly water-soluble drugs, to enhance their dissolution and permeation behaviour is a rapidly growing area in pharmaceutical materials research. Mesoporous silica is a form of silica that is characterised by its mesoporous structure, that is, having pores that range from 2 nm to 50 nm in diameter. Mesoporous silica is a relatively recent development in nanotechnology. Mesoporous silica have a solid framework with porous structure and large surface area, which allows the attachment of different functional group for targeted the drug moiety to a particular site. Mesoporous silica has demonstrated excellent properties to enhance the dissolution rate of poorly water-soluble drugs. Pore diameter, pore volume and surface area are key parameters for controlling drug loading and release from mesoporous carriers. Kinetic studies to date have

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reported a biphasic release profile from mesoporous silica. Pore diameter, pore volume and surface area are key parameters for controlling drug loading and release from mesoporous carriers. It has been widely reported that mesoporous silica can act as a solubility enhancer by adsorbing and stabilizing active pharmaceutical ingredients (APIs) in the amorphous form within the porous network Many times surfactants may also use in the formation of mesoporous silica. Surfactants like cetyl alcohol, sorbitan monostearate, stearyl alcohol, tween80, polysorbate, etc. In contrast, by using mesoporous silica containing drug and carrier could serve as a promising method to solve solubility problem.

Application of Mesoporous Silica: -

1) It is used for targeted drug delivery
2) In removal of heavy metal ion from waste water using modified silica
3) Removal of volatile organic carbons from indoor air using porous silica
4) For improving bioavailability of poorly water soluble drug molecules
5) Enzyme Encapsulation into MS for bio catalysis
6) It is used as diagnostic agents, used for various infection.
7) Encapsulation of pharmaceutical drugs, proteins, & other biological molecules.

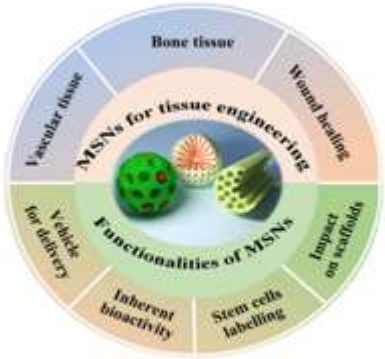

Fig no. 1

Fig no. 2

Synthesis on Mesoporous Silica Material Synthesis: -[7]

Great efforts have been made in the synthesis and use of MSMs in separation, adsorption, catalysis, sensing, and DDSs since the seminal studies, independently published by the two research groups Beck and Kato. Large surface areas are a feature of certain porous materials**,** These porous materials exhibit high biocompatibility, consistent pore size, broad surface areas, and ease of surface functionalization. The three most well-known MSMs are Mobile Composition of Matter-41 (MCM-41) and Santa Barbara Amorphous-15 (SBA-15), both of which have a hexagonal configuration of the mesopores, and MCM-48, which has a cubic layout. MSMs are typically created by condensation and hydrolysis of silica precursors like tetraethoxysilane (TEOS) around micelle templates created by supramolecular self-assemblies of surfactant molecules, followed by calcination or solvent extraction to remove the template**.** The synthesis of MSMs can be explained by two basic methods, namely liquid-crystal templating and cooperative self-assembly of micelle and silica source. MSMs can be made in a variety of sizes, from nanoscale to microscale, with enormous surface areas (between 700 and 1000 m2/g) and pore volumes (between 0.6 and 1 cm2/g).Diverse morphologies (such as spherical, rod, ellipsoid, and platelet) can also be created suited for a variety of biological applications depending on the reaction conditions. While the average MSM hole sizes range from 2 to 5 nm, it is also possible to synthesise pores up to 30 nm, which enables the mesopores to accommodate both tiny molecules and bigger compounds like proteins.

Methods of Incorporation of API in Mesoporous Silica [8,9]

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There are numerous ways to incorporate pharmaceuticals into mesoporous materials, including solvent deposition techniques. mass transfer mediated by the vapour phase Mesoporous silica systems have large surface area and surface energy regardless of the preparation process, and the adsorption of drug molecules on the porous material enables the system to advance to a lower free energy state, or Gibbs free energy is reduced, and this type of systems are stable. In these situations, the medicine is an amorphous material, and it will only solidify if the thermodynamic equilibrium of the system is upset. Space limitations, which prevent the pores from incorporating enough molecules to reach a critical nucleation size, also interfere with crystal development and nucleation in addition to thermodynamic reasons. The loading processimpacts the physical state of hydrophobic drug molecules in ordered mesoporous silica. Adsorption from solution (solvent technique), incipient wetness impregnation, and heating of the drug and the SBA-15 physical mixture were the three loading procedures that were investigated. ITZ was successfully dissolved in SBA-15 by employing the dichloromethane adsorption method and the incipient wetness impregnation technique. At a 20% drug loading, ITZ molecules were molecularly deposited over micro- and mesopores. When a medication is loaded more heavily, an adsorbed layer is created in which ITZ molecules interact in a manner reminiscent to a glassy state. ITZ is best positioned inside the micropores using the incipient wetness impregnation approach and on the mesopores wall using the solvent method. This technique exhibits some advantages, such as rapid extractions, use of small mass of extraction phase, and the use of low sample and organic solvent. Due to the molten state's lower viscosity, ibuprofen was successfully integrated inside the micropores using the melt approach. When subjected to simulated stomach fluid and supersaturation solution, ITZ and ibuprofen both quickly released from SBA-15. The ability to create a homogeneous combination of drug and silica prior to melting depends on the density of the powders and the manner of blending, whereas the loading of ibuprofen and ITZ in ordered mesoporous silica by melt method depends on the drug's molten viscosity. Since the solvent immersion method frequently results in the pores of mesoporous materials not being fully utilised, and as a result, results in a low 89drug loading efficiency and an increase in dissolution rate, some scientists have used supercritical fluid techniques (SCF) to load the drug in mesoporous silica. The volume and depth of ibuprofen that entered the mesoporous silica pores using the SCF technique were found to be greater than those by the solution immersion method. Supercritical carbon dioxide, liquid carbon dioxide, and solvent immersion are examples of drug loading techniques that were successful in transforming crystalline drugs into amorphous ones.

There are various methods for incorporating API into Mesoporous Silica, some of the following methods are explain below they are as follows: -

1)Solvent Immersion Method - The most common technique is an immersion method involving adsorption from organic solution followed by filtration to recover the drug-loaded mesoporous silica.

2)Wetness Impregnation Method - The drug's solubility in the loading solvent is essential because it affects the drug loading efficiency and release. In this method, a high degree of loading can be achieved utilising a concentrated drug solution (typically near to the saturation solubility of the drug). The process of medication synthesis into molecules is easily controlled, and this.

3)Supercritical Fluid Method - The use of SCF drug loading techniques offers many advantages by exploiting the solvent power variation that can be achieved by manipulation of the fluid pressure and temperature in the supercritical region.Carbon dioxide (CO_2) is the most commonly used SCF because it has a low critical point, is non-flammable, recyclable, environmentally benign and inexpensive.

4)Solvent Evaporation Method-The medicine and carrier are dissolved in a volatile solvent and then evaporated in the solvent evaporation process. As organic solvent evaporation happens at low temperatures, this approach can prevent the thermal degradation of medications or carriers.

5)Sol gel Method - In this procedure, the molecular precursor (often metal alkoxide)
is dissolved in water or alcohol and heated and stirred until it gels. Depending on the required qualities and use of the gel, the gel produced by the hydrolysis/alcohololysis process should be dried using the appropriate techniques.

6)Stober method- It is an illustration of a sol-gel process in which a molecular precursor (usually tetraethylorthosilicate) reacts with water in an

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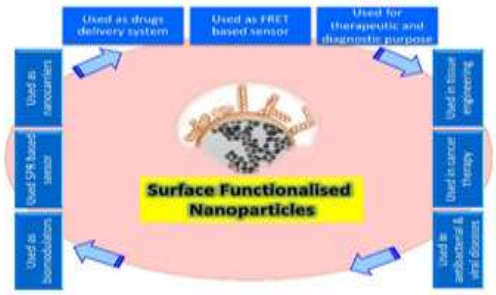
alcoholic solution before the resultant molecules combine to form bigger structure.

7)Surface Functionalization: -It is known that the surface properties of any material have a key role in determining the ir biological fate (e.g., toxicity, biocompatibility, drug loading and release, biodistribution, and cellular internalization). Generally, grafting and co-condensation methods are used for the surface functionalization of MSMs. In the grafting method, the most widely used method, the surface functionalization is carried out after preparation of the MSM using an organosilane surface modifier such as (R′O)3SiR (with diverseorganic groups R). By this method, both the exterior and interior surface of MSM canbe functionalized by the organosilanes.



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EFFECT OF PORE SIZE AND PARTICLE SIZE: -[10,11]

Because the mesopores of mesoporous silica serve as sieves, the pore size can affect how large molecules can be loaded onto the carrier molecule, making it essential for drug loading. Drug molecules should be able to reach the pore, and in general, the ratio of pore diameter to drug molecule size should be greater than 1. Pore diameter to drug molecule size should be greater than 3, which is necessary for high drug loading in the mesoporous material. Shen et al. investigated how ordered mesoporous silica material's pore and particle sizes affected the model medication ibuprofen. Ibuprofen was co-spray dried with mesoporous silica material (MCM-41 and SBA-15) that had varying pore and particle sizes. The physical condition and ibuprofen particle size in the mesoporous structure had an impact on the solid dispersion's dissolving rate, which was significantly increased. In contrast, ibuprofen had a slower rate of dissolution than SBA-15 and MCM-41 when it was co-spray dried with SBA-15 because the pore size was over 20 nm. The solubility of ibuprofen was not significantly affected by the mesoporous silica particle size. Vallet-Regi create mesoporous silica with a range of pore sizes using the hydrothermal effect and various surfactants. The surfactant template's swelling effect, which ultimately causes the pore size of SBA-15 to increase, has grown from 8.4 mn to 11.4 nm as a result of the rise in pressure. The drug dissolving profile has been discovered to be influenced by the control of pore size and shape in porous silica drug carriers. Drug release can take place over a period of minutes, hours, or even days, depending on the particle size and morphology and pore diameter. Horcajada et al. also examined how the mesoporous silica MCM-41's pore size affected the drug loading of ibuprofen.Using surfactant molecules with varied alkyl chain lengths, MCM-41 was created with various pore diameters. Ibuprofen was adsorbed on mesopores of MCM-41 that had pore sizes ranging from 2.5 nm to 3.6 nm. More ibuprofen molecules were loaded into the carrier with the 3.6 nm pore size (19% wt drug loading) than with the 2.5 nm pore size (11% wt drug loading). Ibuprofen was loaded onto a carrier with 3.6 nm pores, forming a monolayer of drug molecules that completely covered the pore surface and left space in the middle for the drug molecules to diffuse freely. Due to geometrical considerations (steric barrier), the close packing of the drug molecule along the pore wall was prevented as the pore size declined to 2.5 nm. Zhang et al tested the sparingly soluble drug telmisartan on spherical mesoporous silica by increasing the pore size from 3.6 nm to 12.9 nm, increasing the drug loading to 59.7% in the 12.9 nm pore. Random mesoporous silica particulates (Syloid AL-1 and 244) were prepared by Kinnari et al. As a delivery system for ITZ hydrophobic drugs. An immersion drug loading method was used in which the particleswere immersed in concentrated solutions of ITZ in dichloromethane (high and low concentrations). ITZ exists in an amorphous form, greatly enhancing solubility. The amorphous form of ITZ was confirmed by DSC, XPRD, and SEM measurements.

EFFECT OF SOLVENT:-[12]The polarity of the solvent has an impact on drug loading. A low level of drug loading is brought on by competitive adsorption between the drug molecules and dimethyl sulfoxide (DMSO), a strongly polar solvent. Charnay et al. thoroughly investigated how solvents (DMSO, DMF, DMA, ethanol, and

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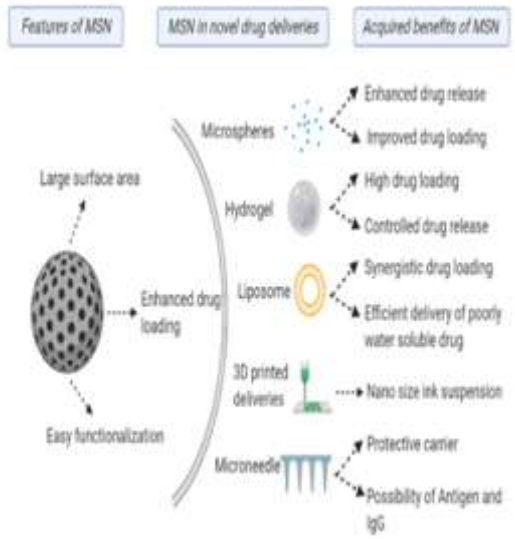

Fig no- 4

hexane) affected the drug loading of poorly solublesubstances. Due to DMA's strong polarity, it was discovered that ibuprofen did not dissolve into the MCM-41 mesoporous material when DMA was utilised as a solvent. Theloading capacity was up to 37% wt in hexane, nevertheless. When loading drugs into mesoporous materials made of TiO2 and Al2O3, the solvent is crucial.

Mesoporous silica materials as dissolution enhancer for PWSDs [13,14,15]

Mesoporous silicas are particularly effective tools for increasing the dissolving rate of PWSDs because they have a number of distinctive and favourable characteristics. We'll go through these variables and how they affect improving dissolution in the following sentences.

I) Specific surface area: - MSMs show high specific surface area. This property is advantageous both for high drug adsorption/loading and for high drug dissolution rate, according to the Nernst and Brunner equation

$$\frac{dm}{dt} = S\frac{D}{h}(Cs - Ct)$$

where m is the mass of dissolved material; t, the time; S is the surface area of the interface between the dissolving solid and the solvent; D is the diffusion coefficient; h, the thickness of the boundary layer of the solvent at the surface of the solid; Cs is the concentration of the substance in the boundary layer that corresponds to the material solubility and Ct is the concentration of the substance in the bulk of the solution. MSMs have a larger specific surface area than non-porous silicas like Cab-O-Sil® (Cabot Corporation Boston, MA USA), Aerosil® (Evonik Industries, Essen, Germany), and HDK® (Wacker, Munich, Germany), which routinely reach and occasionally surpass 1000 m2/g. However, it is crucial to emphasise that even if an increase in surface area promotes both the loading (adsorption) and release (desorption/dissolution), the same processes will still be constrained by the MSM's pore size.

Surface silanols

The presence of silanol groups on the silica surface is the second important aspect of MSMs. The silica surface becomes hydrophilic owing to silanol. They can offer more opportunities for contact with drug molecules that have been adsorbed, and they may be modified to produce functional groups that can strengthen interactions with inserted guest molecules even more. A larger proportion of siloxanes (associated with exposure to higher temperatures) renders the material surface more hydrophobic. The relative amount of silanol (Si-OH) and siloxane (Si-O-Si) groups is tied to the thermal history of the product. As a result, heat treatment can essentially be used to modify the material's hydrophobicity. Pyridine adsorption has been used to distinguish between single, hydrogen-bonded, and germinal silanol on the surface of MCM.The key component of silica as an effective adsorbent material is its surface silanols, which can interact through hydrogen bonds with the proton donor/acceptor groups of the molecules trapped inside the pores. However, when water is present, these weak connections between silanols and the adsorbed chemical may be disrupted, leading to a rapid release of the loaded compound as single molecules.

Pore size: -

The high pore volume and appropriate pore size in the molecular range of MSMs are another important characteristic. Drug molecules are essentially kept in a sub micrometric space to prevent crystallisation because they are adsorbed inside pores that are only 10 times wider than the drug molecules. The drug shows a quicker dissolution in this state than in its crystalline form.

Pore structure: -

Another property of ordered MSMs that contributes to the improvement of dissolving rate is

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the presence of uniformly sized pores that ensure the homogeneity and consistency of drug adsorption and release. The square root of a time-dependent process based on Fickian diffusion can be used to characterise the release kinetics of a medicine from insoluble porous materials using an adaption of the Higuchi model**.**

$$\mathbf{Q = \frac{\sqrt{D\epsilon}}{\tau}\ (2\ A - \epsilon\ Cs - Cs\ t}$$

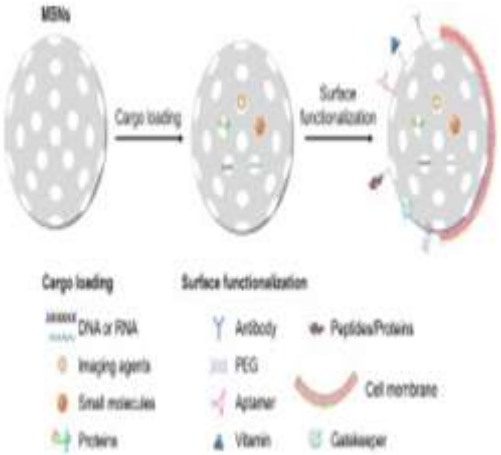
The tortuosity factor (τ), which accounts for the extra distance a solute must travel due to its tortuous path within the matrix, the fractional porosity (pore volume/total material volume) (ϵ), the immersion time (t), the solubility of the drug in the fluid (Cs), the initial drug concentration in the matrix (A), and the drug's diffusion coefficient in the medium where the carrier is immersed are all factors that affect the release, or Q. As more parameters can be defined, the release becomes more predictable for MSMs because and can be more or less controlled. Unfortunately, the Higuchi equation does not directly apply to MSMs employed as drug carrier matrixes since amorphous silica is not water insoluble.

Effect of surface area on dissolution rate: -[16,17]

Kumar et al. evaluated the release of aceclofenac from materials of the MCM-41 type with different surface areas and porosities. No relevant correlation between surface area and dissolution enhancement could be detected until the surface area reached a limiting amount. This might be explained by effective surface area, the real factor controlling the rate of dissolution. According to studies, the drug was disseminated over a silica carrier's substantial surface area at the molecular, supramolecular, or particle levels. Further increases in carrier surface area may not result in further subdivision of the drug due to the presence of increased cohesive forces/surface tension among the drug particles, and consequently, the effective surface area available for in vitro dissolution.

Influence of surface functionalization on drug dissolution rate: -[18,19]

Surface functionalization is a regularly sought approach to \towards the controlled release capabilities of MSMs by inducing particular \sinteractions between the functional groups on the carrier surface \sand the integrated guest molecule. Due to this, only a small number of examples of functionalized ordered mesoporous materials were studied for increasing drug dissolution rate, often aiming for a delayed release rate. To induce specific host-guest interactions with drug molecules carrying acidic groups, for instance, functional groups such as (basic) NH2 on the surface of mesoporous silica are added, or vice versa (COOH-functionalization for primarily basic drug molecules).Strong interactions are preferred during the loading step in order to stabilise the drug in its amorphous form, whereas strong repulsion is preferred during the release step in order to quickly release the drug from the carrier matrix.This is feasible because loading is frequently carried out under non-polar circumstances, whereas release must necessarily occur under aqueous conditions, where various interactions become more obvious. Electrostatic interactions are the longest-ranged forces in aqueous conditions, while intramolecular interactions like hydrogen bonding are typically used at the loading step. Since the majority of drugs are weak acids or bases and the silica surface may have residual silanols in addition to being functionalized with acidic or basic groups, these must be taken into account when describing the release behaviour of almost any drug. By delaying the wetting by an aqueous solvent and enhancing the hydrolytic stability of the silica matrix, non-ionizable surface groups, for instance, can be used to hydrophobize the silica surface in order to delay the release.



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II. CONCLUSION: -[20]

MSMs have a number of highly advantageous qualities that can be used to improve the dissolution of drugs that aren't easily soluble. The dissolution enhancement effect of MSMs has become quite apparent over the past 15 years, but predicting it requires an intricate interplay of many difficult-to-isolate parameters. Based on existing

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theories\sand accumulated studies on specifically synthesised MSMs, a decisive\series of parameters has, nevertheless, been identified. Strong drug-carrier connections (during loading), pore sizes large enough to allow for optimal water penetration into the pore system yet tiny enough to prevent crystallization, and 3D connectivity being favoured over cylindrical pores from the perspective of release are a few examples. The loading procedure will have implications for the resultant loading degree \as well as localization of drug inside the pore system, which, in \turn, may affect wetting. Hence, the constricted pore space for microscopic mesopores restricting water penetration as well as the excess of hydrophobic molecules on the surface have an impact on wetting behaviour. In order to avoid drug fractions on the outside of the particle, which have a tendency to be quickly recrystallized and may be encouraged if excessive loading degrees are sought after, loading conditions must be regulated. Since the majority of studies on the topic to date have been conducted quite randomly with regard to the materials and parameters chosen for study, it is still challenging to draw any broad conclusions about the relationships between important material parameters and release behaviour. As a result, more systematic investigations are required to separate the contributions of these parameters while assessing potential (if any) interactions between the parameters in specific real-world in vivo circumstances. The first-in-man proof-of-concept study, which was just published, is very encouraging because it supports MSMs' ability to increase bioavailability and spur further advancements in this field.

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